

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants : Tetsuo NAGANO et al.

Group Art Unit: 1797

Appln. No. : 10/531,664

(U.S. National Phase of PCT/JP2003/013179)

Examiner: Fritchman

I.A. Filed : October 15, 2003

Conf. No: 1923

For : REAGENTS FOR THE MEASUREMENT OF PEROXYNITRITES

APPEAL BRIEF UNDER 37 C.F.R. § 41.37

Commissioner for Patents
U.S. Patent and Trademark Office
Customer Service Window, Mail Stop Appeal Brief-Patents
Randolph Building
401 Dulany Street
Alexandria, VA 22314

Sir :

This appeal is under 35 U.S.C. 134 from the decision of the Examiner finally rejecting claims 2 and 3 as forth in the Final Office Action dated May 14, 2009.

A Notice of Appeal to the May 14, 2009 Final has been filed on November 16, 2009 (November 14, 2009 being a Saturday) so that the time for filing an Appeal Brief extends until January 16, 2010.

Appellant hereby requests an extension of time for five months to extend the period for filing the Appeal Brief until June 16, 2010, and have submitted a formal Request for Extension of Time for five months accompanied by the government fee on June 15, 2010. However, if for any reason any extension of time and/or any fee is necessary to maintain the pendency of the application, including any extension of time and/or any appeal fee, this is an express request for any required extension of time and authorization to charge any necessary fee to Deposit Account No. 19-0089.

The requisite fee under 37 C.F.R. 41.20(b)(2) in the amount of \$540.00 for the filing of the Appeal Brief is being paid herewith.

As noted above, if for any reason any extension of time and/or any fee is required to maintain the pendency of the application, including any extension of time and/or appeal fee, authorization is hereby provided to charge any required fee, including any fee for the Appeal Brief and any necessary extension of time fee to Deposit Account No. 19-0089.

(I) REAL PARTY IN INTEREST

The real party in interest is Tetsuo NAGANO and Sekisui Medical Co., Ltd. by an assignment from the inventors to Tetsuo NAGANO and Daiichi Pure Chemicals Co., Ltd. recorded February 23, 2006, at Reel 017284, Frame 0643 (5 pages), and by a change of name from Daiichi Pure Chemicals Co., Ltd. to Sekisui Medical Co., Ltd. recorded December 23, 2009, at Reel 023698, Frame 0483 (23 pages).

(II) RELATED APPEALS AND INTERFERENCES

None

There are no pending related appeals and/or interferences.

(III) STATUS OF CLAIMS

The status of the claims is as follows:

Claim 1 is canceled, and claims 2 and 3 are pending in this application and are under appeal.

Of the pending claims, claims 2 and 3 have been finally rejected in the Final Office Action dated May 14, 2009, and are under appeal.

(IV) STATUS OF AMENDMENTS

The appeal is based upon finally rejected claims. An Amendment to the Final Office Action dated May 14, 2009, was filed November 25, 2009 following a November 18, 2009 telephone interview. A first Advisory Action, dated December 21, 2009, indicated that for purposes of appeal the amendment filed November 25, 2009 would not be entered and claims 2 and 3 are rejected. However, a second Advisory Action, dated January 15, 2010, indicated that for purposes of appeal, the amendment filed November 25, 2009 will be entered, and claims 2 and 3 are rejected as explained in the attachment to the Advisory Action.

An amendment was filed February 9, 2010 to correct an error in claim 3. A third Advisory Action, dated February 24, 2010, indicated that for purposes of appeal, the amendment filed February 9, 2010 will be entered, and claims 2 and 3 are rejected.

On June 15, 2010, a Request for Extension of Time for five months, and a Cover Letter Submitting Terminal Disclaimer Under 37 C.F.R. 41.33 and a Terminal Disclaimer accompanied by the government fee were submitted with respect to U.S. Patent No. 7,378,282, which is used in an obviousness-type double patenting rejection. It is assumed that the Terminal Disclaimer will be entered so that the rejection based upon U.S. Patent No. 7,378,282 is moot.

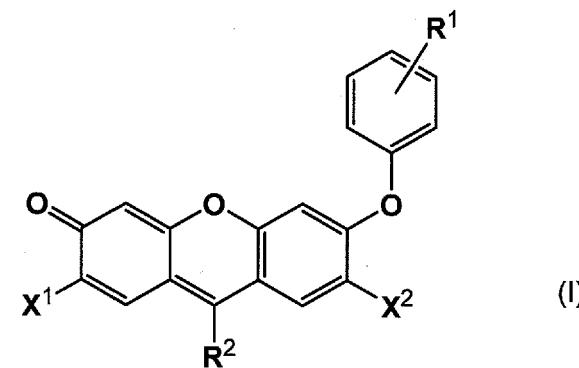
(V) SUMMARY OF THE CLAIMED SUBJECT MATTER

The following description is made with respect to the independent claim and includes references to particular parts of the specification. As such, the following is merely exemplary and is not a surrender of other aspects of the present invention that are also enabled by the present specification and that are directed to equivalent methods within the scope of the claims.

Independent Claim 3

Independent claim 3 recites a method for specifically measuring peroxynitrite (e.g., page 2, lines 16-24), which comprises:

(A) reacting a compound represented by the following formula (I) or a salt thereof and peroxynitrite (e.g., page 2, line 25 to page 3, line 15), the compound or a salt thereof not having substantial reactivity with superoxide and/or NO so that the compound or a salt thereof can specifically measure the peroxynitrite even in the presence of superoxide and/or NO (e.g., page 2, line 16-24, and page 5, line 24 to page 6, line 1, and page 8, lines 13-20 and Table on page 8)



wherein R¹ represents a substituted or unsubstituted amino group, or hydroxy group; R² represents a 2-carboxyphenyl group which may be substituted; and X¹ and X² independently represent hydrogen atom, or a halogen atom; and

(B) measuring fluorescence of a dephenylated compound or a salt thereof produced in
(A) (e.g., page 3, lines 7-15).

(VI) GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

(a) Claims 2 and 3 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 01/64664 to Nagano (using EP 1 260 580 A1 as English version) as evidenced by US 2002/0182736 A1 to Aldini et al. (hereinafter "Aldini").

(b) Claims 2-3 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 5 and 13-14 of U.S. Patent No. 7,087,766 (hereinafter "the '766 patent") as evidenced by US 2002/0182736 A1 to Aldini.

(c) Claims 2-3 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-2 of U.S. Patent No. 7,378,282 (hereinafter "the '282 patent") as evidenced by US 2002/0182736 A1 to Aldini.

(VII) ARGUMENT

(I) Traversal of rejection of claims 2 and 3 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nagano (using EP 1 260 580 A1 as English version) as evidenced by Aldini.

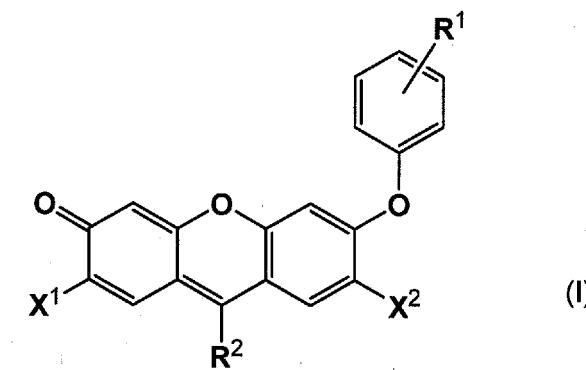
(a) Claims 2 and 3 are not properly rejected under 35 U.S.C. 103(a) as being unpatentable over Nagano as evidenced by Aldini.

(A) Arguments for Independent Claim 3

The rejection of independent claim 3 under 35 U.S.C. 103(a) as being unpatentable over Nagano as evidenced by Aldini is in error, the decision of the Examiner to reject this claim should be reversed, and the application should be remanded to the Examiner.

Appellant's independent claim 1 is directed to a method for specifically measuring peroxynitrite, which comprises:

(A) reacting a compound represented by the following formula (I) or a salt thereof and peroxynitrite, the compound or a salt thereof not having substantial reactivity with superoxide and/or NO so that the compound or a salt thereof can specifically measure the peroxynitrite even in the presence of superoxide and/or NO,



wherein R¹ represents a substituted or unsubstituted amino group, or hydroxy group; R² represents a 2-carboxyphenyl group which may be substituted; and X¹ and X² independently represent hydrogen atom, or a halogen atom; and

(B) measuring fluorescence of a dephenylated compound or a salt thereof produced in (A).

Initially, Appellant notes that the '766 patent, which is being used in an obviousness-type double patenting rejection (that will be discussed *infra*) is the national stage of Nagano. Thus, as an initial matter, Appellant notes that it is not clear why the rejection is using EP 1 260 580 A1 when the '766 patent indicates on its face that it is a national stage of WO 01/64664.

Regarding the merits of the rejection, Appellant submits that this ground of rejection is without appropriate basis, and should be withdrawn.

A review of Appellant's originally filed application reveals, as disclosed in the specification, beginning at page 1, third full paragraph, peroxynitrite (ONOO⁻) is a typical substance among RNS, and is produced by a reaction of NO and superoxide. Reaction rate of this production reaction is mostly limited by diffusion, and when superoxide produced by NADPH oxidase or the like and NO produced by NO synthetase (NOS) coexist, ONOO⁻ is immediately produced. ONOO⁻ has high oxidation ability, for example, it achieves hydroxylation of an aromatic ring, and has characteristic reactivities such as, for example, efficient nitration of tyrosine.

It is further disclosed that examples of the methods for detecting ONOO⁻ developed so far include (1) a method of performing staining by using an antibody directed to nitrotyrosine produced by nitration of tyrosine, and (2) a method of detecting singlet oxygen produced by reaction of ONOO⁻ and H₂O₂ on the basis of light emission at 1.3 μm. It is disclosed that

although method (1) achieves high specificity and has been widely used, the method has a problem in that ONOO⁻ cannot be detected in real time by applying the method to a living cell system, because staining should be performed with antibodies. In addition to the aforementioned two methods, it is also disclosed that (3) a chemiluminescence method using luminol, and (4) a fluorometric detection method using a fluorescence probe to detect overall active oxygen species such as 2',7'-dichlorodihydrofluorescein (DCFH) have been used. **However, these methods fail to achieve specificity, and therefore reliable detection cannot be expected even if various inhibitors are used. For example, it is disclosed that in the method (4), DCFH reacts with both of NO and superoxide to give an increase in fluorescence, and therefore it is impossible to distinguish whether ONOO⁻ is detected, or NO or superoxide is detected.**

Reference is also made in the originally filed application to WO 01/64664 (which is used in the present rejection) for the fact that arylated fluorescein derivatives are known to be useful reagents for measuring active oxygen (International Patent Publication WO01/64664). **However, it is disclosed that this publication neither suggests nor teaches that the fluorescein derivatives have reactivity with peroxynitrite let alone specificity for peroxynitrite in the presence of NO or superoxide.**

Still further, **Appellant's originally filed application includes disclosure of the unexpected nature of the inventive subject matter recited by Appellant including the specific measurement of peroxynitrite even in the presence of superoxide and NO, which are precursors of peroxynitrite, as see, for example, the second full paragraph on page 2, and page 5, the paragraph beginning at the bottom of the page. Moreover, Examples of the unexpected specific measurement of peroxynitrite in the presence of superoxide and NO are provided in Applicants' originally filed specification.** In this regard, attention is directed

to Appellant's Examples wherein the results are shown in Table 1. As disclosed in Example 1, the measuring reagents of the present invention (HPF and APF) gave an increase in fluorescence by the reaction with peroxynitrite, whilst the reagents did not react with superoxide or NO, and gave substantially no increase of fluorescence. DCFH greatly increased fluorescence by the reaction with peroxynitrite, and it also increased fluorescence by the reactions with both of superoxide and NO. These results are disclosed as revealing that peroxynitrite alone is successfully measured specifically by using the measuring reagent of the present invention without being affected by superoxide or NO.

In contrast, to the showings in Appellant's originally filed application, WO 01/64664, which is specifically discussed in Appellant's originally filed application and includes the inventors of the present application, does not teach or suggest a method of measuring peroxynitrite, nor does WO 01/64664 teach or suggest a method of measuring peroxynitrite without being affected by NO or superoxide.

The rejection does not provide any suitable teaching or suggestion for measuring peroxynitrite, and certainly does not show any expectation of success in specifically measuring peroxynitrite when it would be expected that NO and superoxide would be expected to interfere with such measurement.

The rejection appears to rely upon Aldini to try and establish obviousness of measuring peroxynitrite. However, Aldini is directed to a method of evaluation of lipid antioxidant activity of a sample by accurately measuring the antioxidant activity of both the lipid compartment and the aqueous compartment. Aldini merely mentions various free radicals or other reactive oxygen species in paragraphs [0046] and [0048], which include both peroxynitrite and superoxide anion radical and nitric oxide radical. However, Aldini does not teach or suggest the specific reaction

with peroxy nitrite in the manner recited in Applicants' claims that provides the specific measure of peroxy nitrite. At most, Aldini is further evidence of Applicants' unexpected specific measurement of peroxy nitrite. In this regard, the rejection explicitly asserts that it would be expected that compounds as recited by Appellant would be expected to measure unlimited types of reactive oxygen species, and therefore would not be expected to specifically measure peroxy nitrite.

The Examiner's Interview Summary mailed November 23, 2009, discusses anticipation of a species that is at once envisaged by a genus. However, in the present situation, the rejection is not an anticipation rejection. In this regard, Appellant notes an anticipation rejection is not of record and has been withdrawn because Nagano does not disclose measuring peroxy nitrite. Moreover, the measurement of peroxy nitrite in the manner recited in Appellant's independent claim 3 is not "readily envisaged". Nagano provides disclosure of measuring various types of reactive oxygen's including superoxide and nitrogen monoxide, as see Table 1 of Nagano. However, Nagano does not teach or suggest measuring peroxy nitrite let alone specifically measuring peroxy nitrite in the presence of superoxide or NO. Certainly, this is unexpected and not readily envisaged from any disclosure in Nagano.

Moreover, in the Advisory Action dated January 15, 2010, the Examiner makes assertions of inherency of singlet oxygen in peroxy nitrite (apparently intending peroxy nitrite). However, the Examiner does not point to any inherency of measuring peroxy nitrite but tries to establish obviousness of measuring peroxy nitrite when no showing of peroxy nitrite measurement can be shown in the prior art.

Accordingly, the rejection of record is without appropriate basis and should be withdrawn.

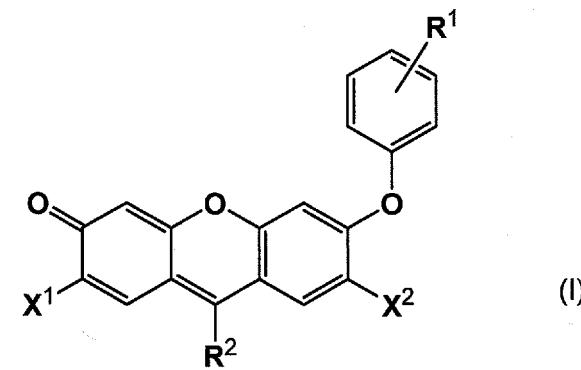
(B) Arguments for Dependent Claim 2

The rejection of dependent claim 2 under 35 U.S.C. 103(a) as being unpatentable over Nagano as evidenced by Aldini is in error, the decision of the Examiner to reject this claim should be reversed, and the application should be remanded to the Examiner.

Appellant's dependent claim 2 further patentably defines independent claim 3 by reciting that the compound represented by formula (I) is 2-[6-(4'-hydroxy)phenoxy-3H-xanthen-3-on-9-yl]benzoic acid, or 2-[6-(4'-amino)phenoxy-3H-xanthen-3-on-9-yl]benzoic acid. Therefore, claim 2 is patentable for at least the reasons set forth with respect to independent claim 3, and for the additional reasons set forth herein.

There is no teaching or suggestion in Nagano of a method for specifically measuring peroxynitrite, which comprises:

(A) reacting a compound represented by the following formula (I) or a salt thereof and peroxynitrite, the compound or a salt thereof not having substantial reactivity with superoxide and/or NO so that the compound or a salt thereof can specifically measure the peroxynitrite even in the presence of superoxide and/or NO,



wherein R¹ represents a substituted or unsubstituted amino group, or hydroxy group; R² represents a 2-carboxyphenyl group which may be substituted; and X¹ and X² independently represent hydrogen atom, or a halogen atom; and

(B) measuring fluorescence of a dephenylated compound or a salt thereof produced in (A), wherein the compound is 2-[6-(4'-hydroxy)phenoxy-3H-xanthen-3-on-9-yl]benzoic acid, or 2-[6-(4'-amino)phenoxy-3H-xanthen-3-on-9-yl]benzoic acid.

As illustrated in Appellant's originally filed application, as see, for example, Appellant's specification at page 5, beginning at line 6, and the Table 1 of Appellant's Example, these particularly preferred compounds yield unexpected results by specifically measuring peroxynitrites in the presence of superoxide or NO.

The rejection does not provide any suitable teaching or suggestion for measuring peroxynitrite, and certainly does not show any expectation of success in specifically measuring peroxynitrite when it would be expected that NO and superoxide would be expected to interfere with such measurement.

The rejection appears to rely upon Aldini to try and establish obviousness of measuring peroxynitrite. However, Aldini is directed to a method of evaluation of lipid antioxidant activity of a sample by accurately measuring the antioxidant activity of both the lipid compartment and the aqueous compartment. Aldini merely mentions various free radicals or other reactive oxygen species in paragraphs [0046] and [0048], which include both peroxynitrite and superoxide anion radical and nitric oxide radical. However, Aldini does not teach or suggest the specific reaction with peroxynitrite in the manner recited in Applicants' claims that provides the specific measure of peroxynitrite. At most, Aldini is further evidence of Applicants' unexpected specific measurement of peroxynitrite. In this regard, the rejection explicitly asserts that it would be

expected that compounds as recited by Appellant would be expected to measure unlimited types of reactive oxygen species, and therefore would not be expected to specifically measure peroxynitrite.

Accordingly, the rejection of record is without appropriate basis and should be withdrawn.

(II) Traversal of rejection of claims 2 and 3 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 5 and 13-14 of the '766 patent as evidenced by Aldini.

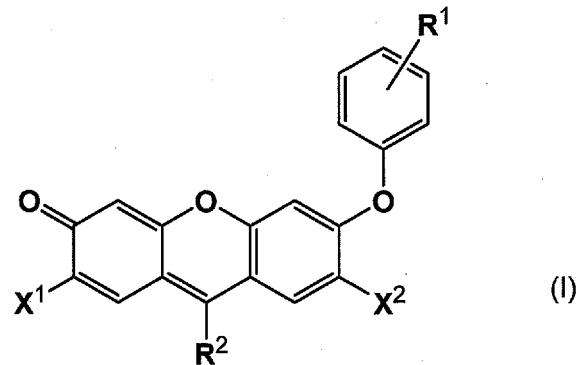
(a) Claims 2 and 3 are not properly rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 5 and 13-14 of U.S. Patent No. 7,087,766 as evidenced by Aldini.

(A) Arguments for Independent Claim 3

The rejection of independent claim 3 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 5 and 13-14 of the '766 patent as evidenced by Aldini is in error, the decision of the Examiner to reject this claim should be reversed, and the application should be remanded to the Examiner.

Appellant's independent claim 3 is directed to a method for specifically measuring peroxynitrite, which comprises:

(A) reacting a compound represented by the following formula (I) or a salt thereof and peroxynitrite, the compound or a salt thereof not having substantial reactivity with superoxide and/or NO so that the compound or a salt thereof can specifically measure the peroxynitrite even in the presence of superoxide and/or NO,



wherein R¹ represents a substituted or unsubstituted amino group, or hydroxy group; R² represents a 2-carboxyphenyl group which may be substituted; and X¹ and X² independently represent hydrogen atom, or a halogen atom; and

(B) measuring fluorescence of a dephenylated compound or a salt thereof produced in
(A).

Initially, Appellant notes that the '766 patent is the national stage of WO 01/64664. Accordingly, for at least the reasons set forth above, the '766 patent does not render obvious the subject matter recited in Applicants' independent claim 3.

The rejection claim that:

Claims 2-3 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 5 and 13-14 of U.S. Patent No. 7,087,766 as evidenced by Aldini et al. (US 2002/0182736). Although the conflicting claims are not identical, they are not patentably distinct from each other because the '766 compounds ss-1F and ss-3F anticipate the compounds HPF and APF, respectively, of Formula (I) as claimed in claims 2 and 3.

Regarding the method claim 3, one of ordinary skill in the art would expect that the compounds of '766 to react with reactive oxygen species other than the expressed examples, including the reactive oxygen species peroxy nitrite ion. Regarding '766 patent claims 5 and 13-14, '766 does not expressly provide an example using ss-1F or ss-3F to measure peroxy nitrites ion. However, Nagano discloses a method for measuring reactive oxygen using compounds ss-1 F and ss-3F and teaches that “[t]he types of reactive oxygens which are measurable by the agent of the present invention are not particularly limited.” ([0020]). It is well known among those with ordinary skill in the art that peroxy nitrite ion contains reactive oxygen, as evidenced by Aldini et al. ([0046], [0048]). Therefore, one of ordinary skill in the art would expect that compounds ss-1F and ss-3F would measure peroxy nitrite ion with a reasonable likelihood of success.

In contrast to the assertions in the rejection, claims 5 and 13-14 of the '766 patent are merely directed to the measurement of reactive oxygen using the compound or a salt thereof according to claim 1, the compound or a salt thereof according to claim 2, or the compound or a salt thereof according to claim 3, respectively. The rejection makes the assertion that, “the '766 compounds ss-1 F and ss-3F anticipate the compounds HPF and APF, respectively, of Formula (I) as claimed in claims 2 and 3.” However, the '766 compounds ss-1F and ss-3F are not recited in the asserted claims of the '766 patent. Accordingly, the basis for the rejection is improper at least for this reason.

Moreover, the rejection asserts that ss-1F and ss-3F of the '766 patent would be expected to equally measure any form of reactive oxygen. However, the claims of the '766 patent do not teach or suggest any desirability of measuring peroxy nitrite or the surprising capability of specifically measuring peroxy nitrite without being affected by NO or superoxide. Accordingly, the claims of the '766 patent, whether taken alone or considered with Aldini, would not arrive at Appellant's claimed subject matter.

Still further, a review of Appellant's originally filed application reveals, as disclosed in the specification, beginning at page 1, third full paragraph, peroxy nitrite (ONOO⁻) is a typical

substance among RNS, and is produced by a reaction of NO and superoxide. Reaction rate of this production reaction is mostly limited by diffusion, and when superoxide produced by NADPH oxidase or the like and NO produced by NO synthetase (NOS) coexist, ONOO⁻ is immediately produced. ONOO⁻ has high oxidation ability, for example, it achieves hydroxylation of an aromatic ring, and has characteristic reactivities such as, for example, efficient nitration of tyrosine.

It is further disclosed that examples of the methods for detecting ONOO⁻ developed so far include (1) a method of performing staining by using an antibody directed to nitrotyrosine produced by nitration of tyrosine, and (2) a method of detecting singlet oxygen produced by reaction of ONOO⁻ and H₂O₂ on the basis of light emission at 1.3 μm. It is disclosed that although method (1) achieves high specificity and has been widely used, the method has a problem in that ONOO⁻ cannot be detected in real time by applying the method to a living cell system, because staining should be performed with antibodies. In addition to the aforementioned two methods, it is also disclosed that (3) a chemiluminescence method using luminol, and (4) a fluorometric detection method using a fluorescence probe to detect overall active oxygen species such as 2',7'-dichlorodihydrofluorescein (DCFH) have been used. **However, these methods fail to achieve specificity, and therefore reliable detection cannot be expected even if various inhibitors are used. For example, it is disclosed that in the method (4), DCFH reacts with both of NO and superoxide to give an increase in fluorescence, and therefore it is impossible to distinguish whether ONOO⁻ is detected, or NO or superoxide is detected.**

Reference is also made in the originally filed application to WO 01/64664 (which is the International Application of the national stage patent used in the present rejection) for the fact that arylated fluorescein derivatives are known to be useful reagents for measuring active

oxygen. However, it is disclosed that this publication neither suggests nor teaches that the fluorescein derivatives have reactivity with peroxy nitrite.

Still further, Appellant's originally filed application includes disclosure of the inventive subject matter recited by Appellant including the specific measurement of peroxy nitrite even in the presence of superoxide and NO, which are precursors of peroxy nitrite, as see, for example, the second full paragraph on page 2, and page 5, the paragraph beginning at the bottom of the page. Moreover, Examples of the unexpected specific measurement of peroxy nitrite in the presence of superoxide and NO are provided in Applicants' originally filed specification. In this regard, attention is directed to Appellant's Examples wherein the results are shown in Table 1. As disclosed in Example 1, the measuring reagents of the present invention (HPF and APF) gave an increase in fluorescence by the reaction with peroxy nitrite, whilst the reagents did not react with superoxide or NO, and gave substantially no increase of fluorescence. DCFH greatly increased fluorescence by the reaction with peroxy nitrite, and it also increased fluorescence by the reactions with both of superoxide and NO. These results are disclosed as revealing that peroxy nitrite alone is successfully measured specifically by using the measuring reagent of the present invention without being affected by superoxide or NO.

In contrast, to the showings in Appellant's originally filed application, WO 01/64664, which is specifically discussed in Appellant's originally filed application and includes the inventors of the present application (or its national stage '766 patent), does not teach or suggest a method of measuring peroxy nitrite, nor does WO 01/64664 (or its national stage '766 patent teach or suggest a method of measuring peroxy nitrite without being affected by NO or superoxide.

The rejection does not provide any suitable teaching or suggestion for measuring peroxy nitrite, and certainly does not show any expectation of success in specifically measuring peroxy nitrite when it would be expected that NO and superoxide would be expected to interfere with such measurement.

The rejection appears to rely upon Aldini to try and establish obviousness of measuring peroxy nitrite. However, Aldini is directed to a method of evaluation of lipid antioxidant activity of a sample by accurately measuring the antioxidant activity of both the lipid compartment and the aqueous compartment. Aldini merely mentions various free radicals or other reactive oxygen species in paragraphs [0046] and [0048], which include both peroxy nitrite and superoxide anion radical and nitric oxide radical. However, Aldini does not teach or suggest the specific reaction with peroxy nitrite in the manner recited in Applicants' claims that provides the specific measure of peroxy nitrite. At most, Aldini is further evidence of Applicants' unexpected specific measurement of peroxy nitrite. In this regard, the rejection explicitly asserts that it would be expected that compounds as recited by Appellant would be expected to measure unlimited types of reactive oxygen species, and therefore would not be expected to specifically measure peroxy nitrite.

In the Advisory Action dated January 15, 2010, the Examiner makes assertions of inherency of singlet oxygen in peroxy nitrile (apparently intending peroxy nitrite). However, the Examiner does not point to any inherency of measuring peroxy nitrite but tries to establish obviousness of measuring peroxy nitrite when no showing of peroxy nitrite measurement is shown.

Accordingly, the rejection of record is without appropriate basis and should be withdrawn.

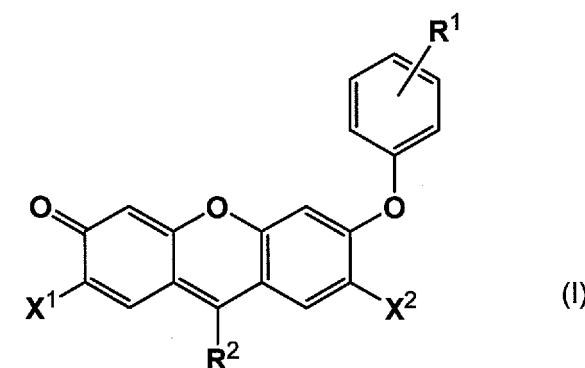
(B) Arguments for Dependent Claim 2

The rejection of dependent claim 2 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 5 and 13-14 of the '766 patent as evidenced by Aldini is in error, the decision of the Examiner to reject this claim should be reversed, and the application should be remanded to the Examiner.

Appellant's dependent claim 2 further patentably defines independent claim 3 by reciting that the compound represented by formula (I) is 2-[6-(4'-hydroxy)phenoxy-3H-xanthen-3-on-9-yl]benzoic acid, or 2-[6-(4'-amino)phenoxy-3H-xanthen-3-on-9-yl]benzoic acid. Therefore, claim 2 is patentable for at least the reasons set forth with respect to independent claim 3, and for the additional reasons set forth herein.

There is no teaching or suggestion in the '766 patent either alone or in view of Aldini of a method for specifically measuring peroxynitrite, which comprises:

(A) reacting a compound represented by the following formula (I) or a salt thereof and peroxynitrite, the compound or a salt thereof not having substantial reactivity with superoxide and/or NO so that the compound or a salt thereof can specifically measure the peroxynitrite even in the presence of superoxide and/or NO,



wherein R¹ represents a substituted or unsubstituted amino group, or hydroxy group; R² represents a 2-carboxyphenyl group which may be substituted; and X¹ and X² independently represent hydrogen atom, or a halogen atom; and

(B) measuring fluorescence of a dephenylated compound or a salt thereof produced in (A), wherein the compound is 2-[6-(4'-hydroxy)phenoxy-3H-xanthen-3-on-9-yl]benzoic acid, or 2-[6-(4'-amino)phenoxy-3H-xanthen-3-on-9-yl]benzoic acid.

As illustrated in Appellant's originally filed application, as see, for example, Appellant's specification at page 5, beginning at line 6, and the Table 1 of Appellant's Example, these particularly preferred compounds yield unexpected results by specifically measuring peroxynitrites in the presence of superoxide or NO.

In contrast, the '766 patent which is the national stage of WO 01/64664, which is specifically discussed in Appellant's originally filed application and includes the inventors of the present application, does not teach or suggest a method of measuring peroxynitrite, nor does WO 01/64664 teach or suggest a method of measuring peroxynitrite without being affected by NO or superoxide.

Moreover, the claims referenced in the rejection of the '766 patent do not recite the compounds recited in Appellant's claim 2.

The rejection does not provide any suitable teaching or suggestion for measuring peroxynitrite, and certainly does not show any expectation of success in specifically measuring peroxynitrite when it would be expected that NO and superoxide would be expected to interfere with such measurement.

The rejection appears to rely upon Aldini to try and establish obviousness of measuring peroxynitrite. However, Aldini is directed to a method of evaluation of lipid antioxidant activity

of a sample by accurately measuring the antioxidant activity of both the lipid compartment and the aqueous compartment. Aldini merely mentions various free radicals or other reactive oxygen species in paragraphs [0046] and [0048], which include both peroxynitrite and superoxide anion radical and nitric oxide radical. However, Aldini does not teach or suggest the specific reaction with peroxynitrite in the manner recited in Applicants' claims that provides the specific measure of peroxynitrite. At most, Aldini is further evidence of Applicants' unexpected specific measurement of peroxynitrite. In this regard, the rejection explicitly asserts that it would be expected that compounds as recited by Appellant would be expected to measure unlimited types of reactive oxygen species, and therefore would not be expected to specifically measure peroxynitrite.

Accordingly, the rejection of record is without appropriate basis and should be withdrawn.

(III) Traversal of rejection of claims 2 and 3 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 2 of the '282 patent as evidenced by Aldini.

(a) Claims 2 and 3 are not properly rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 2 of the '282 patent as evidenced by Aldini.

As noted in section (IV) Status of Amendments, on June 15, 2010, a Terminal Disclaimer accompanied by the government fee and a Request for Extension of Time for five months were submitted with respect to the '282 patent. The Terminal Disclaimer has been filed to reduce issues for consideration by the Examiner and the Board, and it is assumed that the Terminal

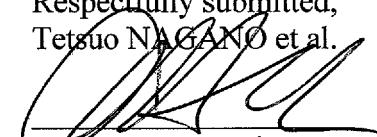
Disclaimer will be entered so that the rejection based upon 'the 282 patent is moot. Accordingly, as this rejection is no longer applicable and should be withdrawn, arguments for patentability are not included herein.

Accordingly, withdrawal of the rejection is respectfully requested.

CONCLUSION

For the reasons set forth above, it is respectfully submitted that the Examiner has failed to establish a *prima facie* case of obviousness, which is a prerequisite for maintaining a rejection under 35 U.S.C. 103(a) and under the doctrine of non-statutory obviousness-type double patenting. The Board is, therefore, respectfully requested to reverse the Final Rejection, and to allow the application to issue in its present form.

Respectfully submitted,
Tetsuo NAGANO et al.



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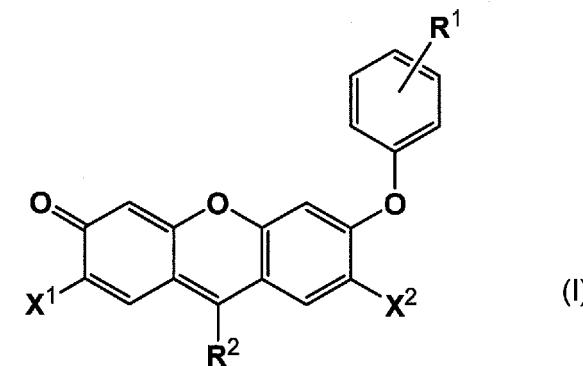
Attachments: (VIII) Claims Appendix
(IX) Evidence Appendix
(X) Related Proceedings Appendix

(VIII) CLAIMS APPENDIX**CLAIMS ON APPEAL**

2. The method according to claim 3, wherein the compound represented by formula (I) is 2-[6-(4'-hydroxy)phenoxy-3H-xanthen-3-on-9-yl]benzoic acid, or 2-[6-(4'-amino)phenoxy-3H-xanthen-3-on-9-yl]benzoic acid.

3. A method for specifically measuring peroxynitrite, which comprises:

(A) reacting a compound represented by the following formula (I) or a salt thereof and peroxynitrite, the compound or a salt thereof not having substantial reactivity with superoxide and/or NO so that the compound or a salt thereof can specifically measure the peroxynitrite even in the presence of superoxide and/or NO,



wherein R¹ represents a substituted or unsubstituted amino group, or hydroxy group; R² represents a 2-carboxyphenyl group which may be substituted; and X¹ and X² independently represent hydrogen atom, or a halogen atom; and

(B) measuring fluorescence of a dephenylated compound or a salt thereof produced in (A).

(IX) Evidence Appendix

Copies of evidence entered by the Examiner and relied upon by Appellant in the appeal along with statements setting from where in the record that evidence was entered in the record by the Examiner.

- (a) WO 01/64664 to Nagano et al. ("Examiner assumes that the English version of WO01/64664 in the form of EP 1 260 508 A1 is a direct translation of WO01/64664 and therefore examiner references the EP publication.") – entered in the record in initialed Form PTO-1449 attached to Office Action mailed October 10, 2008.
- (b) US 2002/0182736 A1 to Aldini et al. – entered in the record in Form PTO-892 attached to the 1449 attached to Final Office Action mailed May 14, 2009.
- (c) U.S. Patent No. 7,087,766 to Nagano et al. – entered in the record in the nonstatutory obviousness-type double patenting rejection set forth in the Office Action mailed October 10, 2008.
- (d) U.S. Patent No. 7,378,282 to Setsukinai et al. – entered in the record in the nonstatutory obviousness-type double patenting rejection set forth in the Office Action mailed October 10, 2008.

(X) Related Proceedings Appendix

None